IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

In re application of
Yasushi OCHIAI et al.
Application No.: 10/091,559 Art Unit: 1615
Filed: March 7, 2002 Examiner: RACHEL M. BENNET
For: METHOD OF MANUFACTURING DRUG GRANULES, THE DRUG GRANULES AND PHARMACEUTICAL PREPARATION CONTAINING THE DRUG GRANULES

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Declaration Under 37 CFR § 1.132

Sir:

In connection with the above-identified U.S. patent application, I, Yasushi Ochiai, a citizen of Japan and residing at 203, 5-3-15, Furuedai, Suita-Shi, Osaka, 565-0874, Japan, say and declare as follows:

1. I received a Master's degree from the Department of Polymer Chemistry of the Faculty of Engineering , Kyoto University in Japan in 1992.

2. I have been working at Sumitomo Pharmaceuticals Research Center since 1992. I have been studying controlled release oral formulations or preparations.

3. I am a co-author of the paper of the list attached.

4. I am one of the inventors in U.S. Serial Number 10/091,559 and I am very familiar with the subject matter thereof and have been researching the subject matter thereof since 2001.

5. Materials
All raw materials were commercially available in Japan.
Lysine hydrochloride: L-Lysine monohydrochloride (Kyowa Hakko Kogyo Co. Ltd.)
Microcrystalline cellulose: Avicel PH-101 (Asahi Kasei Chemicals)

6. Experiment

6.1. Granulation and Polishing

Polished lysine hydrochloride granule was prepared by the method described in US 5,300,318.

Equipment used

Mixer: Crypto mixer (Crypto Peerless Ltd.)

Extruder: Basket type extrusion granulator HU-G (Hata Iron Works)

Priller: Marumerizer QFMN-400(Fuji Paudal Co. Ltd.)

Fluidized bed dryer: Spray granulator LABO-1 (Powrex Corporation)

a) Dough preparation

Into the mixer were introduced:

Lysine hydrochloride	1275g
Microcrystalline cellulose	225g

These were homogenized dry for 10 minutes. An aqueous solution of binder was introduced, prepared beforehand and made up of:

Hydroxypropyl methyl cellulose	46g
Purified water	614g

After complete addition these were stirred for 2 minutes

was 70 degrees Celsius. When the outlet air temperature reached 50 degrees Celsius, drying was finished.

e) Polishing

460g of the non-polished granules with a diameter of between 0.59 and 0.84mm were introduced into the Spray granulator LABO-1. Fluidization was set in motion and the polishing solution was sprayed. The polishing operation was carried out under the following conditions:

Polishing ratio 10%	
Experiment No.	1
Granule charge	460g
Air flow	$100m^3/h$
Air inlet temperature	40 degrees Celsius
Spraying pressure	1.6bar
Rate of spraying solution	13g/min
Polishing solution	
Lysine hydrochloride	46g
Purified water	115g
Solution temperature	Room temperature

Polishing ratio 20%	
Experiment No.	2

agent. I decided to use methacrylic acid copolymer (Polyquid PA30S) as an enteric agent.

400g of the 10% polished granule with a diameter of between 0.59 and 0.84mm were introduced into Multiplex MP-01. The Coating operation was carried out under the following conditions similar to the method of US 5,300,318. The coating ratio was generally about 40% for enteric coating pharmaceuticals.

Equipment used
Multiplex MP-01 Wurster type (Powrex Corporation)
Coating conditions:

Experiment No.	3
10% polishing granule charge	400g
Air flow	60m^3/h
Air inlet temperature	70 degrees Celsius
Spraying pressure	3.0bar
Rate of spraying solution	12.6g/min
Coating solution	
Polyquid PA30S	540g (solid:162g)
DKester F-50P	9g
PEG6000P	9g
Purified water	522g
Coating solution temperature	Room temperature

6.3. Admixing

0.1g of Magnesium stearate was added to 10g of the coated granules obtained in Experiment No.3 and mixed thoroughly.

6.4. Tableting

2g of the above mixture was compressed using a tableting apparatus (tableting tester SK-02, Sankyo Pio-tech Co., Ltd.) at tableting pressure of 1.5 ton.

6.5. Measurement of granular strength

The granular strength was measured using a table-top material tester (EZ Test-20N, Shimadzu Corporation) as described in Evaluation test 3 of the specification. One lysine granule each from the non-polished lysine granules and polished lysine granules was placed on

diameter of 5mm, the granules were compressed in a compression mode at 0.5mm/min and the maximum peak was taken as the strength. The measurement was repeated 3 times and the measures were averaged. The strength was divided by the sectional area.

6.6. SEM (Scanning Electron Microscope)

The image of SEM was obtained by the below conditions.

<SEM conditions>

Machine: Scanning Electron Microscope S－530 (Hitachi High-Technologies)

Ion sputter E－1030 (Hitachi High-Technologies)

Thickness of vacuum evaporation: 15nm

Sample: non-polished Lysine granule, 10% polishing Lysine granule, 20% polishing Lysine granule, coated Lysine granule with Polyquid PA30S, non-coated metformin granule of the present invention, coated metformin granule with Aquacoat of Example 4 in the present invention, non-coated carbocisteine granule of the present invention, Lysine tablet obtained in the above mentioned manner, and metformin tablet of Example 4 in the present invention

6.7. Dissolution test

The dissolution of lysine from coated granule and tablet obtained in the above mentioned was evaluated according to Japan pharmacopoeia, method 2 (Paddle Method) of dissolution test.

<Analysis conditions>

Dissolution tester NTR-6100A (Toyama Sangyo Co., Ltd.)

Test dissolution: pH1.2

Amount of solution: 900ml

Temperature of solution: 37 degrees Celsius

Rate of rotation: 100rev/min

Sampling amount: 5ml

Measurement method: absorption at 210 nm of sample solution was measured by UV-Visible Spectrophotometer UV-1600 (Shimadzu Corporation).

The dissolution of metformin from the granules of Example 3 in the present invention

7.1. Granular strength

Table 1 is a result of the measurement of the Lysine granules.

Table 1 Granular Strength of Lysine Granule

	(gf/mm^2)
Non-polished granule	304
10% polishing granule	387
20% polishing granule	453

The granules of US 5,300,318 have a much smaller strength than that of granules of the present invention.

7.2. SEM

Fig. 1 - Surface of Metformin Granule

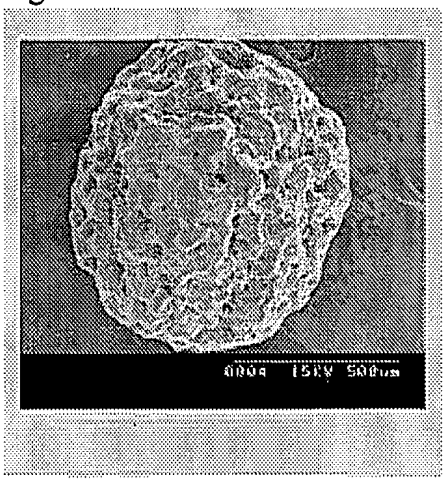


Fig. 2 - Magnification of Fig. 1

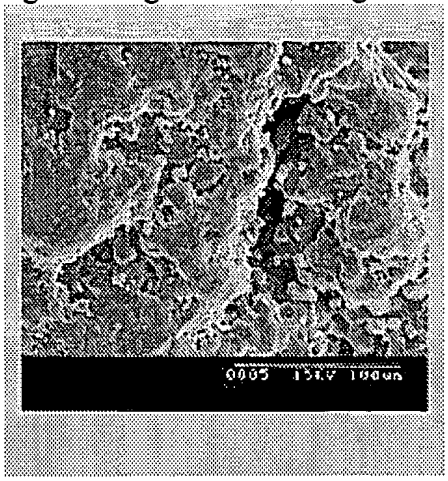


Fig. 3 - Cross-section of Metformin Granule

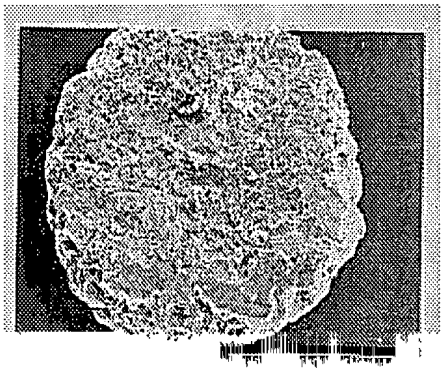


Fig. 4 - Magnification of Fig. 3

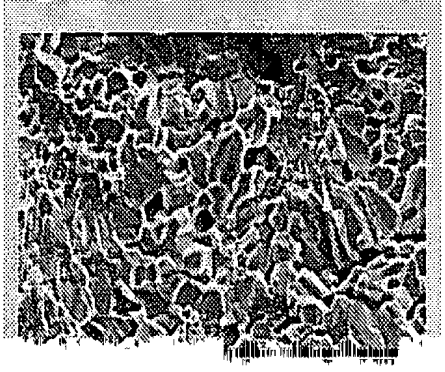


Fig. 5 - Surface of Carbocisteine Granule

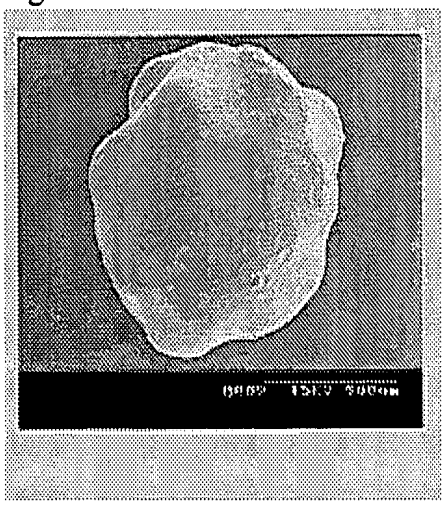


Fig. 6 - Magnification of Fig. 5

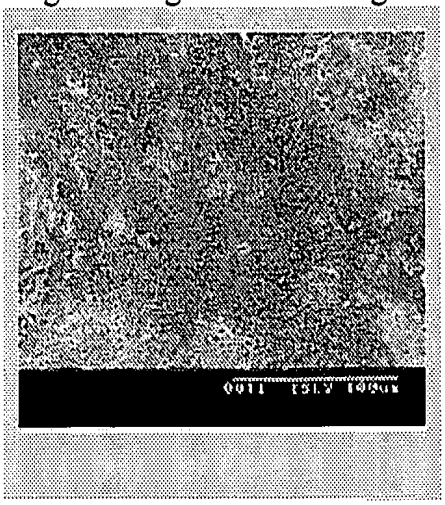


Fig. 7 – Cross-section of Carbocisteine Granule

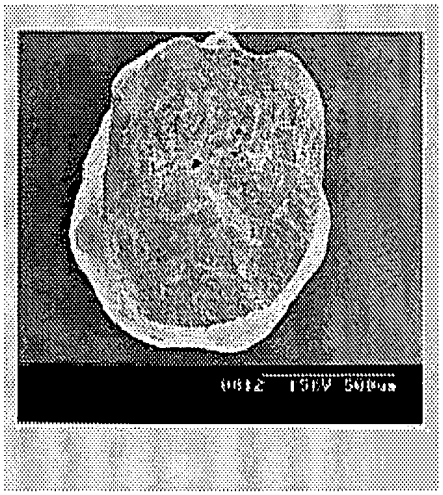


Fig. 8 -Magnification of Fig. 7

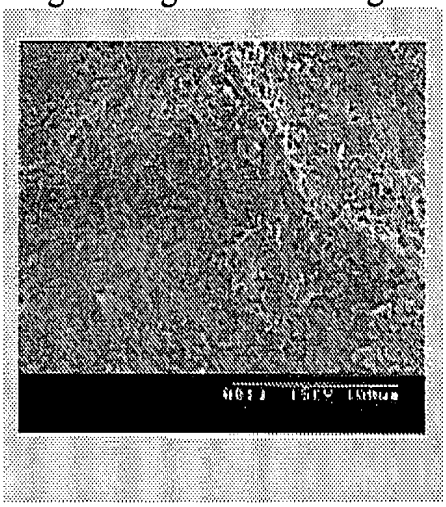


Fig. 9 - Surface of Non-polished Lysine Granule

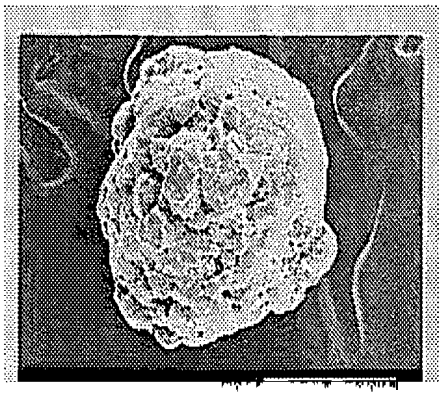


Fig. 10 - Magnification of Fig. 9

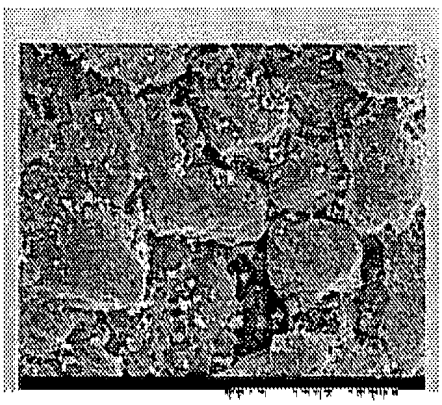


Fig. 11 – Cross-section of Non-polished Lysine granule

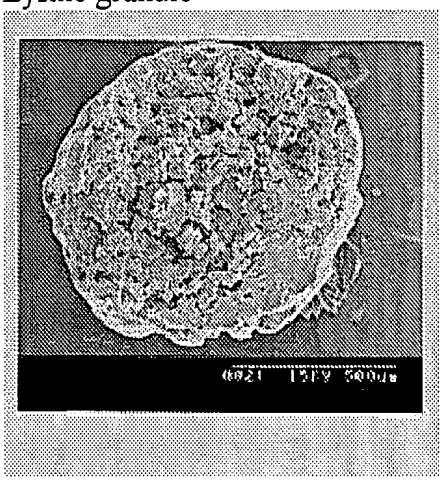


Fig. 12 - Magnification of Fig. 11

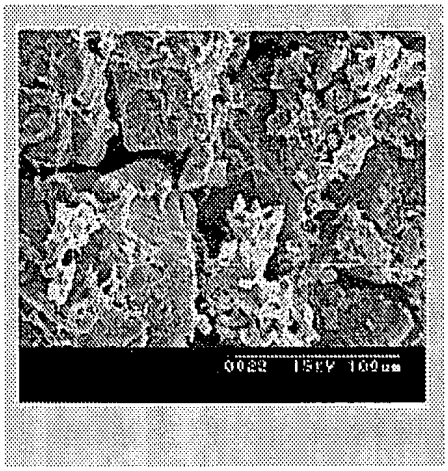


Fig. 13 - Surface of Lysine 10% Polishing Granule

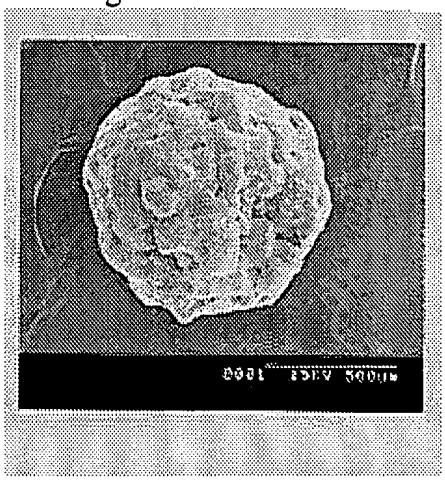


Fig. 14 - Magnification of Fig. 13

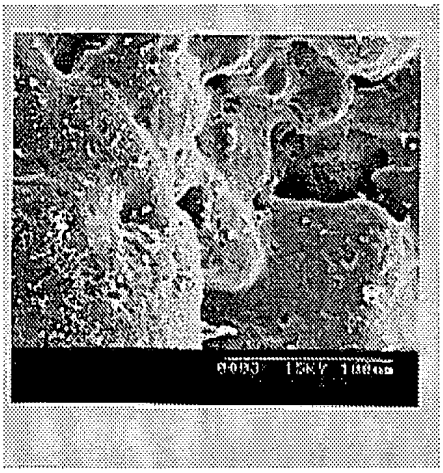


Fig. 15 – Cross-section of Lysine 10% Polishing Granule

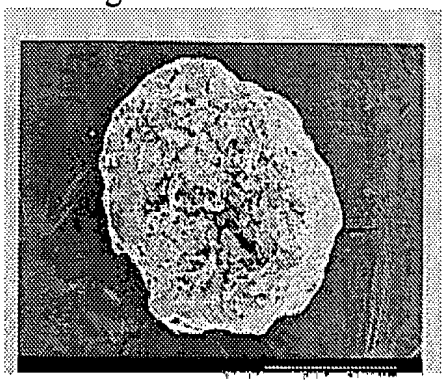


Fig. 16 - Magnification of Fig. 15

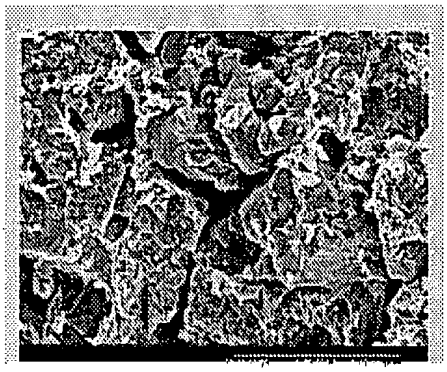


Fig. 17 - Surface of Lysine 20% Polishing Granule

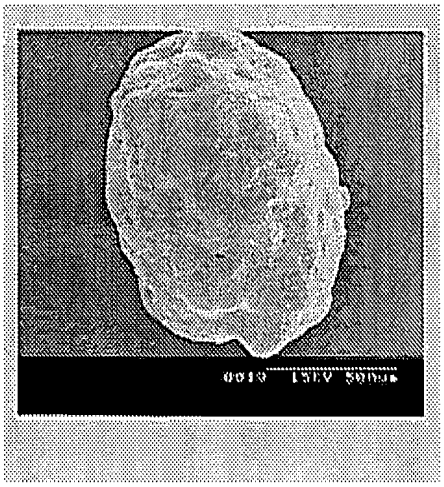


Fig. 18 - Magnification of Fig. 17

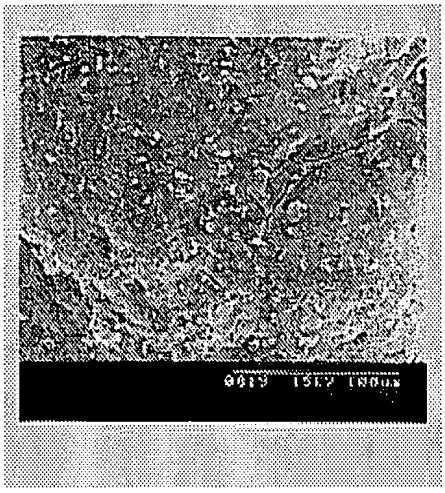


Fig. 19 - Cross-section of Lysine 20% Polishing Granule

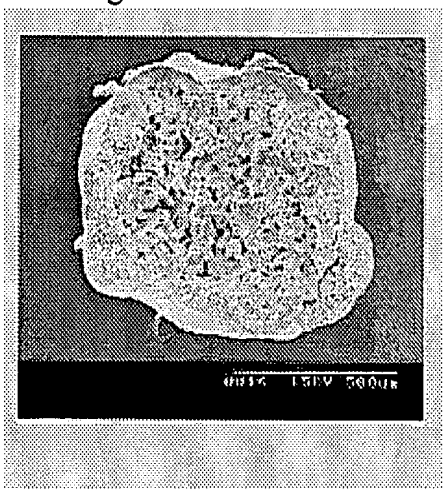


Fig. 20 - Magnification of Fig. 19

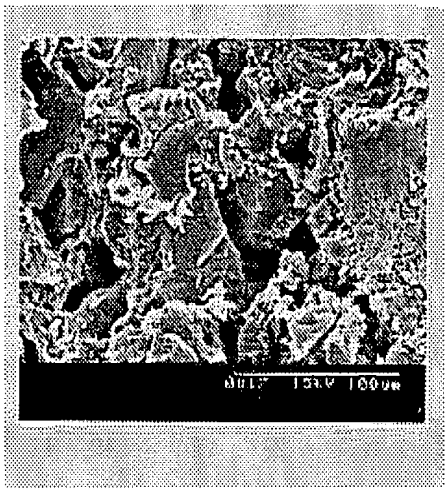


Fig. 21 - Coating Lysine Granule

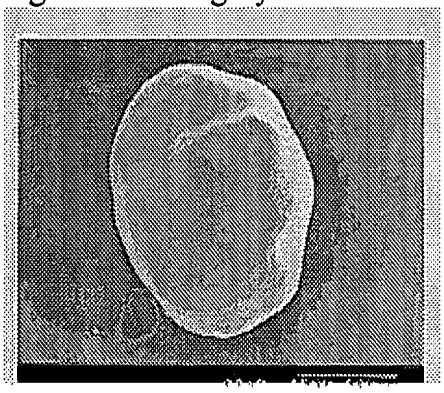


Fig. 22 - Coating Metformin Granule

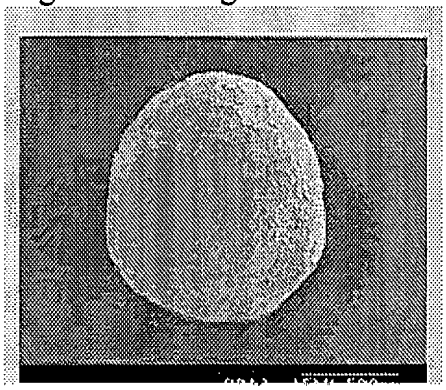


Fig. 23 - Surface of Lysine Tablet

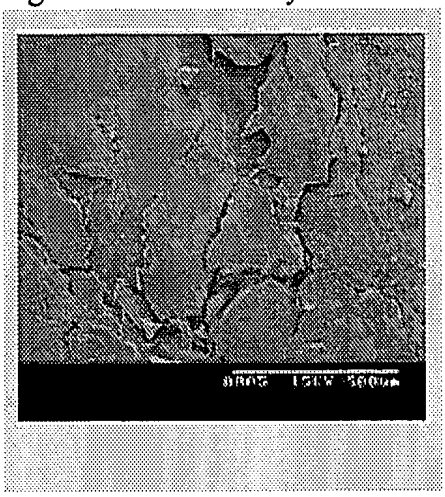


Fig. 24 – Cross-section of Lysine Tablet

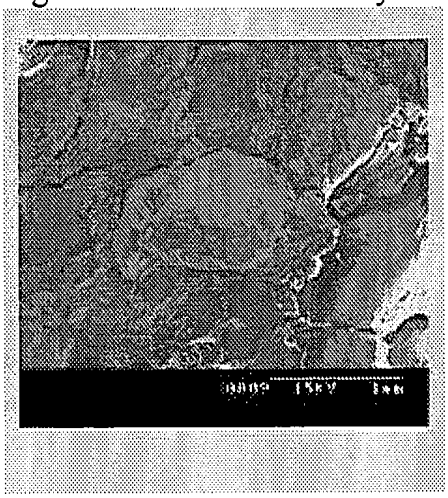


Fig. 25 - Magnification of Cross-section of Lysine Tablet (Fig. 24)

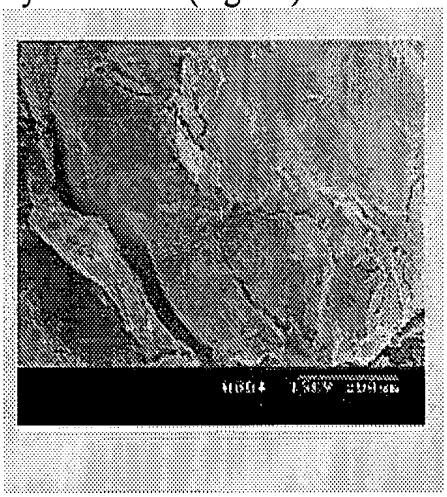


Fig. - 26 Surface of Metformin Tablet

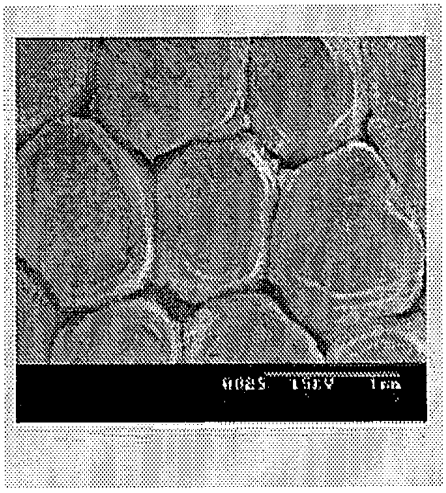
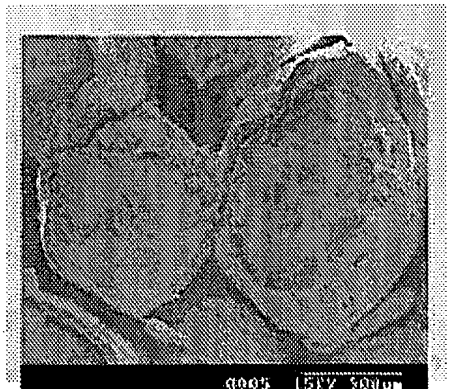


Fig. 27 – Cross-section of Metformin Tablet



Figures 1-8 show that the granules of the present invention have homogeneous structure.

Figures 9-12 shows that the granules of US 5,300,318 having porous and non-homogeneous structures.

Figures 13-20 show the lysine granules after polishing have smooth surfaces, but the inner parts of the polished granules still have porous and non-homogeneous structures.

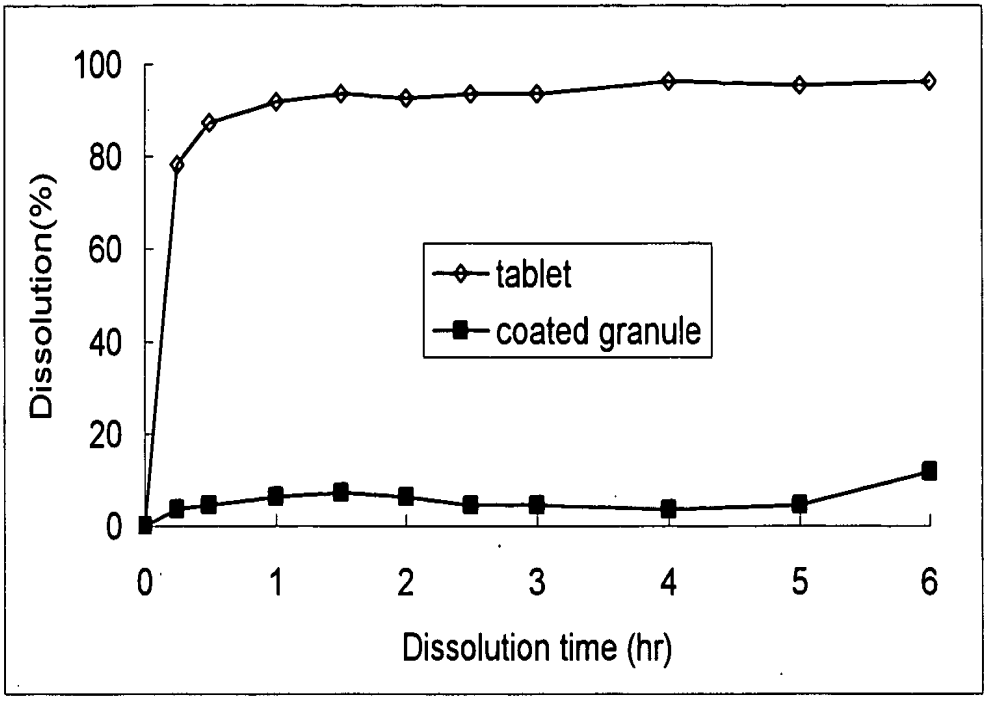
Figure 21 shows coated granules of US 5,300,318 having smooth and homogeneous surfaces.

Figure 22 shows the present invention having smooth and homogeneous surfaces.

Figure 23 shows the surface of tablet made of the coated Lysine granule of US 5,300,318 and Figure 24 shows the cross section of the tablet (The granules are broken by tableting and the shape of the granule is changed completely.). Figure 25 shows magnification of the cross section. The film of the coated Lysine granule in the tablet has cracks.

Figures 26-27 show the surface and the cross section of tablet of the present invention. Th[illegible]e of the granules of the present invention is shown to be maintained after tableting

Figure 28



As shown in the graph results of Figure 28, the dissolution of lysine from the coated Lysine granules was very little and that the enteric coating film on the lysine granules functioned appropriately. However, in contrast dissolution from the tablet was very fast, showing that the enteric coating film on the granules in the lysine tablet were broken during tableting.

Figure 29

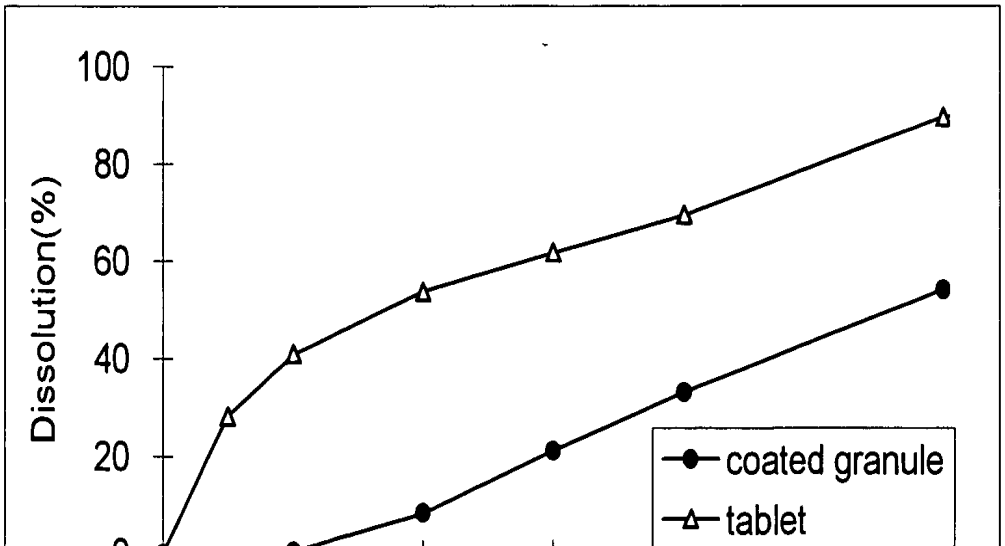
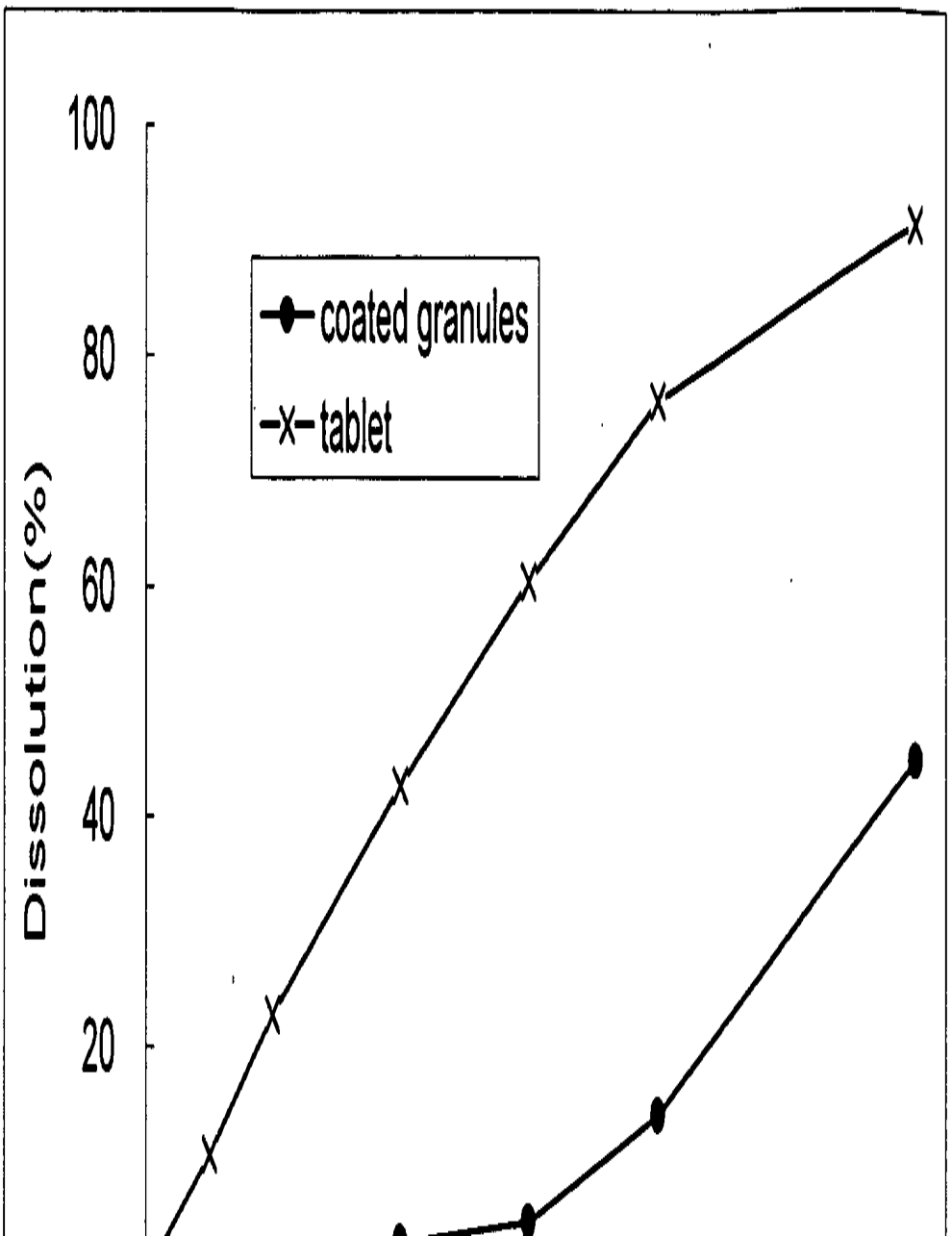


Figure 30



8. Conclusion

The test results provide above show that the granular strength of the present invention is quite distinct and different from that of Pierre et al. (US 5,300,318). The results also show that a difference exists with regard to the inner structure of granules between the present invention and Pierre et al. The difference of granular strength is reflected by the maintaining of the coating film and granule structure after tableting . (*See* Figures 26-27 *verses* Figures 23-25).

Pierre et al. (US 5,300,318) does not provide any suggestion regarding granular strength and/or tableting. In contrast, the present invention provides granules having an sufficient granular strength to be capable of maintaining a coating film during tableting processes, and thereby also allow for the manufacture of tablets from the coated granules having desirable and suitable dissolution characteristics. (*See* Figures 29-30 *verses* Figure 28.)

Based on the above considerations, I submit that one of ordinary skill in the art, even upon considering the disclosure of US 5,300,318 (Pierre et al.), would in no way be motivated to arrive at the instant invention as claimed, or otherwise led to arrive at the instant invention and the unexpected and advantageous properties that are possessed thereby (as evidenced by the above Figures 26-27 and 29-30). I further submit that such test results are completely unexpected to those of ordinary skill in the art.

9. The undersigned declares further that all statement made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that Such willful false statement may jeopardize the validity of above identified application or any patent issuing thereon.

List of Publication

1) pH-sensitive gating by conformational change of polypeptide brush grafted on porous polymer membrane, Ito Y., Ochiai Y., Park YS. and Imanishi Y., J. Am. Chem. Soc. 119, 1619-23, 1997